HIV time hierarchy: Winning the war while, loosing all the battles.

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Abstract

AIDS is the pandemic of our era. A disease that scares us not only because it is fatal but also because its insidious time course makes us all potential carriers long before it hands us our heads in a basket. The strange three stage dynamics of aids is also one of the major puzzles in describing the disease theoretically [1]. Aids starts, like most diseases, in a peak of virus expression[2, 3], which is practically wiped out by the immune system. However it then remains in the body at a low level of expression until later (some time years later) when there is an outbreak of the disease which terminally cripples the immune system causing death from various common pathogens. In this paper we show, using a microscopic simulation, that the time course of AIDS is determined by the interactions of the virus and the immune cells in the shape space of antigens and that it is the virus's ability to move more rapidly in this space (it's high mutability) that causes the time course and eventual 'victory' of the disease. These results open the way for further experimental and therapeutic conclusions in the ongoing battle with the HIV epidemic.

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Introduction:

The natural progression of the Human Immuno-deficiency Virus (HIV) infection varies between individuals, however a general pattern of the progression has been observed (Figure 1).

- Within weeks of infection, a short transient jump of plasma virema (virion concentration in plasma) is seen together with a marked decrease in Immune cell counts (CD4 T Helper cells).
- Partial control of the disease by the immune system ensues, causing variable periods of practically a-symptomatic clinical latency, which can last years. During this period the Immune cell population continues to slowly decline until the immune system is so crippled it can no longer contain the disease.
- A renewed outbreak of the virus which, together with constitutional symptoms and the onslaught by opportunistic diseases, cause death [1].

The dynamics of HIV was traditionally described using simple homogeneous ODEs[5] (for a review see Perelson [6]). This method was enlarged to models considering the spatial structure mainly by Zorzenon dos Santos and Coutinho [2, 3]. Such models consider the importance of the localization of the interactions between the HIV virions and immune cells. Taking into consideration the global features of immune response and the high mutation rate of HIV they described the spatial and temporal interactions of infected and healthy cells in lymphoid tissue in the body.

The methodology used in spatially extended models was limited up to now mainly to cellular automata [2, 3], or to compartmental models [7]. The main advantage of cellular automata is their capacity to emphasize the emergence and the importance of spatial structures. For example the propagation of waves of infection in the lymph nodes, or the creation of immune cell aggregations[2, 3]. Consequently Zorzenon dos Santos and Coutinho, in contradiction with most ODE models, succeeded to reproduce all the stages of HIV evolution, using a single set of rules [3, figure 13 in 2].

The present model is inspired by the observed interesting features in the spatially extended model[2, 3] . Our model acts in the shape space rather than in the physical space and exploits the dynamical implications of the HIV virus 'propagation' in the molecular shape space: The immune system's need to identify the virus's form correctly in the shape space of possible viral and immune

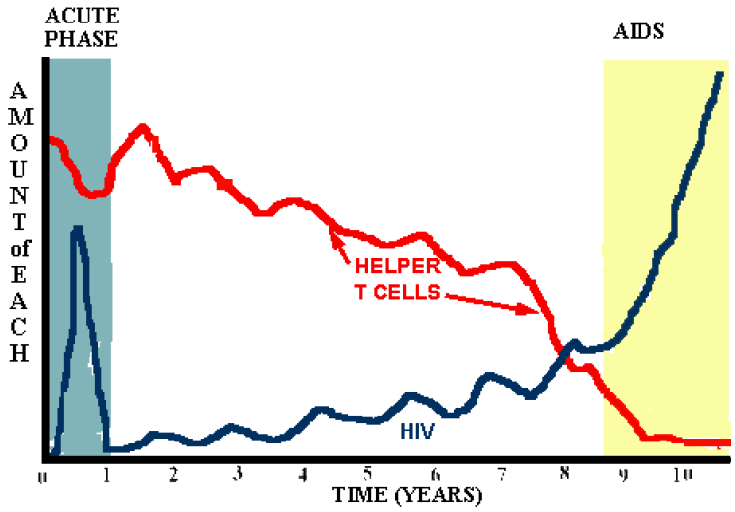

Figure 1: **The typical 3 stage evolution of the HIV illness** - According to the experimental data, the HIV infection evolution presents 3 distinct phases. During the first months after infection, there is an acute phase with a very large increase in the virus population and a corresponding destruction of the immune cells. This ends with the reprise of the immune system to the invasion and the decrease of the virus population to very low values. After the immune systems reprise comes a long period of slowly increasing virus population and slowly decreasing immune cells population. At some stage, the virus population rises exponentially and the immune system collapses (the AIDS phase) resulting in an onslaught of opportunistic diseases and death. (Addapted from picture, Copyright Dr R.E. Hurlbert, from the Washington State University Fundamentals of Microbiology 101 course home page: http://www.wsu.edu:8080/~hurlbert/pages/Chap16.html#STD_intro)[4].

receptor shapes. The main ingredients in our model are the mutations (represented by propagation of the multiplying virions in the structure-less infinite dimensional shape space) and the confrontation with the immune system cells (resulting in the disappearance of the both cells and virions). Our model does not display any geometrical patterns in either space or shape space. In this model we assume that we can average the spatially distributed reactions (as in the ODE approach).

The model presented in the following pages relies on the basic known facts on the immune defense system. The viruses (antigens) have various characteristic geometrical shapes. In order to act against them, the immune system has to 'identify' them by producing cells which contain shapes complementary to the geometry of (parts of) these antigens. Since the immune system does not know a priori what is the characteristic shape of every new invading virus, the immune system generates randomly cells with various shapes. If a cell encounters (by chance) an antigen (virion) with complementary shape, then more cells with characteristic shapes identical to it are produced and a mechanism is triggered for the destruction of all the individuals (virions) belonging to this virus strain (and sharing the same shape)[8].

Usually the destruction mechanism is quite efficient and once a virion is 'identified' by the above random search in the shape space, its fate and the fate of all the virions in the same strain is sealed: they are wiped out by the immune system within days.

With HIV however, the issue is more complicated[2, 3]: Since the virus's replication mechanism is relatively imprecise, as it multiplies it undergoes a large amount of mutations/changes in shape compared to those found in other kinds of virus [9, 10, 11]. Based on empirical and theoretical results in the research of HIV we propose the following scenario. The immune system cells that are complementary to the old shape are ineffective in dealing wiht the new mutant virus strain. The virions belonging to the strain with the new shape can multiply with impunity until a strain of immune cells which fits the new shape is generated by the immune system. Once the Immune system's shape generation process succeeds to produce by chance a immune cell carrying a complementary shape to the new virus strain and this cell encounters (by chance) a virion belonging to the new strain, the new strain is wiped out too (with the exception of the eventual new mutants that again can multiply freely until their new shape is detected by the immune system). The process continues indefinitely with the virus loosing every battle but succeeding to produce increasingly many small populations of new shapes (figure 2)[8, 12, 13, 14, 15, 16] .

The process is compounded by the additional fact that virions can kill directly and indirectly immune cells (whether or not they are of complementary

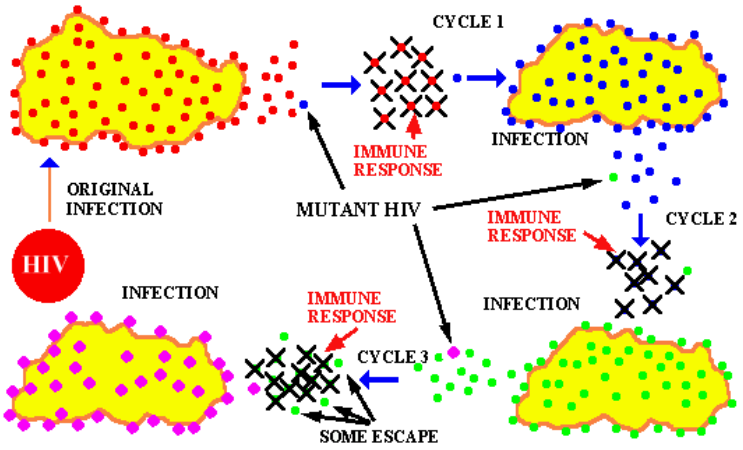

Figure 2: The HIV strains in the primary infection are detected and annihilated by the immune system. However some virions escape the immune system by mutating. While the new population which they engender is also eventually discovered and destroyed by the immune system, their mutating descendants will escape again. These phases of escape and destruction enable the intermittent proliferation of HIV after the immune systems primary response and with it the idiosyncratic time course of HIV infection. (Picture, Copyright Dr R.E. Hurlbert, taken from the Washington State University Fundamentals of Microbiology 101 course home page: http://www.wsu.edu:8080/~hurlbert/pages/Chap16.html#STD_intro[4])

shape)[17].

The immune system continues to win every battle until the increase in production of immune cells with shape complementary to a virus strain is overcome by the rate at which the immune cells are destroyed by various other HIV strains. At this point the immune system has effectively lost the war.

In the rest of the paper we provide a detailed microscopic simulation model [18, 19, 20, 21] which supports this scenario and that fits quite well the known phenomenological data on HIV in terms of the following basic mechanisms:

- The **local** (in shape space) destruction of HIV by the immune system[15].
- The fast mobility of HIV in shape space (high mutation rate)[9, 10].
- The **global** destruction of immune system cells by HIV[17].

1 The Model

We represent the shape space of the virus by a random lattice in which each site (i) has a fixed number of neighbors. Neighboring sites represent shapes that can be reached one from the other by a single base mutation of the virus. The

occupation number on each site (N_{Vi})represents the number of virions with that shape existing in the organism. The immune system cells that recognize that shape are also represented through an occupation number on the same site(N_{Ci}). Note that the existence of a virus and an immune cell on same lattice site does not imply their proximity in real space: Quite to the contrary they might be located in very distant locations in the organism. There is however a small probability that the virus and the corresponding cell will meet and react in real space. Therefore each pair of virion and immune cell located on the same lattice site has a small, but finite probability to react (according to the rules described in detail below).

One represents the eventual mutations of the virus and the immune cells by their rate of diffusion in the shape space (D_V,D_C). More precisely both viruses and immune cells have a certain probability for jumping between neighboring sites.[1]

HIV can replicate in and destroy immune cells. This is irrespective of the cell's characteristic shape. I.e. the virus can destroy immune cells located on sites arbitrarily far away from the site of the virus). In our model we represent this by:

- A virus proliferation rate proportional to the total immune cells population (C_{tot}).
- An immune cell death rate proportional to the total viral population (V_{tot}).

We list bellow the reactions taking place in the model:

1. When an HIV virion and an immune cell reside on the same site the immune cell duplicates with a rate of τ_C. However following realistic biological data, we limit the multiplication rate of the immune cells (to a factor of 3 per day).
2. When an HIV virion and an immune cell reside on the same site the virion is destroyed with a probability rate of d_V.
3. Each HIV virion replicates with a rate ($\tau_V C_{tot}$) proportional to the total number of immune cells.
4. Each immune cell is destroyed with a probability rate ($d_C V_{tot}$) proportional to the total number of virions.
5. New immune cells, with various shapes are created continuously. We represent this by a probability rate (λ) for an immune cell to appear on a random lattice site.

[1] The diffusion rate, and the neighborhood structure implied by the node's connectivity can be different for the virus and for the immune cells

6. Both the immune cells and the HIV virus diffuse slowly in the shape space with rates D_V and D_C .

2 Results

The reactions listed in the previous section lead to the following scenario for the evolution of the HIV infection. The virus enters the body in a high concentration limited to a restricted number of strains. As long as there is no immune cell in the site corresponding to a certain strain, the virions located in this strain site proliferate exponentially. The rise in virus concentration is accompanied by a destruction of random T cells hosting the virus (according to item 4). These T cells can be located anywhere in the lattice. Eventually one of the immune cells generated by the immune system will fall by chance on the site of this strain (according to item 5) . This immune cell will proliferate very fast, since, according to item 1, the proliferation rate increases with the local viral concentration. The resulting high local immune cells concentration will destroy all the virions of this strain (item 2). As a result, after a short period (1-2 month) all the initial strains will be discovered by the immune system and will be destroyed ending the acute phase of the disease. In the absence of virus diffusion in shape space (i.e. mutations), this would stop the disease (Figure 3).

It is the diffusion rate of the virus in shape space (item 6) which is responsible for the continuation of the infection. Before all the initial strains are destroyed, some of the virions have a chance to mutate and escape to lattice points containing no immune cells.

Each of these new lattice points in the shape space will contain a lower concentration of virus than the original infection. Since the probability for the discovery of a virus strain by the immune cells is proportional to the virus strain concentration (according to item 1) the time it will take for the immune system to discover, and destroy these new strains (item 2) will be longer than in the acute phase. By the time these new strains are destroyed some virions from these strains will have diffused to neighboring sites (undergo mutations), and constitute the germs for a new generation of emerging strains. These strains in turn will have the fate of their predecessors in the previous generation. One sees now that one can describe the long-term evolution of the HIV infection as an iterative process. More precisely the long-term evolution will consist of a chain of small infections, each of which is easily defeated by the organism. However after each such infection the number of strains will grow. Therefore even though the number of virions in each strain is always kept under control

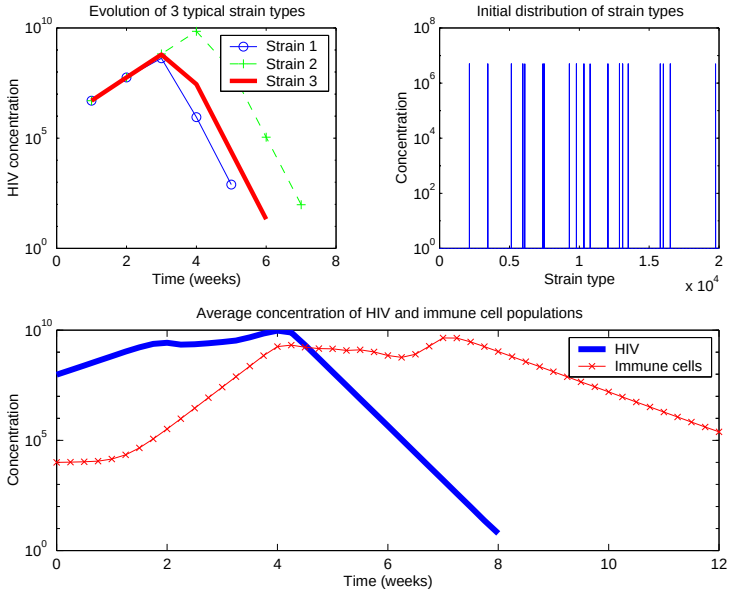

Figure 3: **The acute phase analyzed by strains-** The simulation of the acute phase provides an explanation to the very large peak in the virus population: In HIV infection as opposed to an infection by a single virus strain, the organism has to discover a multitude of strains. The height of the virus population peak is usually dominated not by the average strain population but by the population of the strain which is discovered last by the immune system (and has the longest time to exponentiate). In the simulation the acute phase starts with a constant concentration of HIV distributed between 20 strains (upper right drawing). Each one of these strains activates an immune response and is destroyed (upper left drawing). The average over all strains is the observed average HIV and immune cell concentration (Lower drawing).

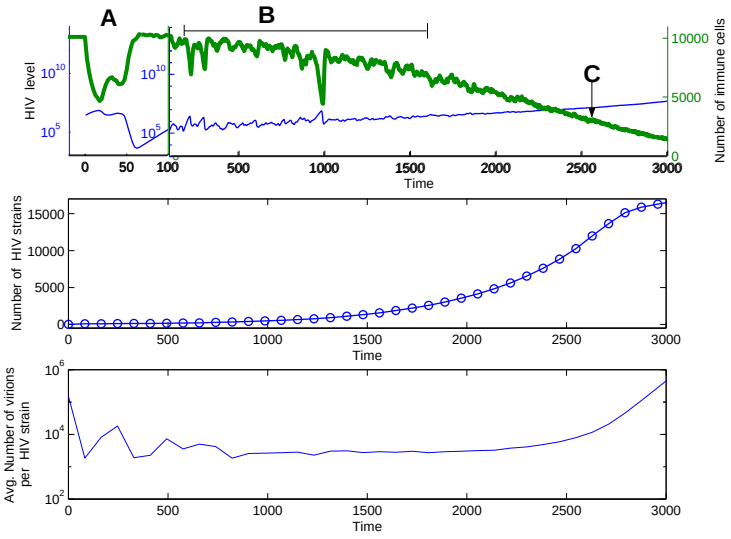

Figure 4: **Typical HIV evolution in our simulation-** In the top part of the figure we see that with our simulation we capture the dynamics found in the empirical data. By comparing with the Fig. 1, one sees that our model reproduces correctly the 3 stages of the disease. The acute phase (A), a phase of chronic latency (B) and finally a renewed outbreak of HIV coupled with the destruction of the immune system (C). Note that the first 100 days are plotted at a different scale. In the two other figures we see, over the progression of the disease, the number of different HIV strains (middle) and the average concentration of viroins per strain (bottom). Together these two graphs strengthen our explanation that the time course of HIV is based on the contradiction in local and globals concentration of HIV - Locally the levels of HIV are kept by the immune system at a minimum far below the level found in the primary infection. Globally, through the rise in the number of strain types, the virus is spreading stochastically through shape space and increasing its numbers by avoiding the local immune attacks.

by the organism, the total amount of virions will stochastically slowly increase. The increase is stochastic, since it depends on the random time it takes the immune system to discover and destroy each new strain. As the number of virions increases, so does the death rate of the immune cells (item 4) . At a certain stage the death rate will be high enough to impair the capacity of the immune system to react locally to new strains. This constitutes the last stage of the disease (Figure 4).

This typical scenario can vary from person to person:

1. The typical case observed in most hosts is a disease composed of 3 stages (Figure 4). The first acute stage is due to the fast proliferation of the original strains before the appropriate immune response is set. This stage

ends when the appropriate immune response to each and every original strains is completed. This stage takes approximately $\lambda*\ln$(Number of original strains) days (see below). This gives an expected number of virions at the peak, which is much higher than in a usual disease (Appendix A) . The latent stage is the stage in which the number of virion strains is limited, and the number of virions in each strain is low. This stage will last as long as the number of strains is much smaller than $\frac{\tau_C}{d_C}$ (Appendix B). When the number of **strains** grows above $\frac{\tau_C}{d_C}$ the last stage of the disease occurs. This is the regime in which the local (in shape space) activation of the immune system by the local virus strain (item 2) becomes lower than the global destruction rate of immune cells by the virions (item 4), and the immune system fails to destroy **locally** (item 4) the existing strains. At this stage many old strains that were kept under control during the previous stages can reappear.

2. If the efficency of immune reaction to HI (items 1 and 2) is high enough, the immune system will manage to defeat the new virus strains fast enough. Thus the average number of strains will stay constant or slowly decrease. In this case the total number of virions will vary around a fixed number, or slowly decrease to 0. This fate can be the one of the long time carriers8[22, 23]. In reality, the total number of virions never decreases to zero, since there are other sources (macrophages, neuronal cells, etc.) that contribute a small number of new virions [22, 24](Figure 5).

3. When, on the other hand, the efficency of immune reaction is low a large number of new strains will be created before the immune cells will finish destroying the virions from the strains of the first infection. In this case the acute phase will directly lead to the death of the host (Figure 6)[22, 25].

The results of our simulations show that although each new strain that emerges is destroyed within a few weeks (like any ordinary disease), the long term evolution of the infection takes years. The time scale that determines the long-term evolution scale is the diffusion (mutation) rate of the virus. The number of new strains growes exponentially with time , but the unit of time in this exponential is the time it takes for a new strain to establish itself i.e. weeks.

One might ask how the scale hierarchy between the cellular interactions (hours) and the evolution of the infection (years) emerges in this model. The answer is the following. The single strain lifetime is determined by an exponential rate proportional to the local interaction rate (hours). This exponent rises to macroscopic virus concentration within weeks. Only when the value of this exponent is high enough does the long-term mechanism of virus mutation

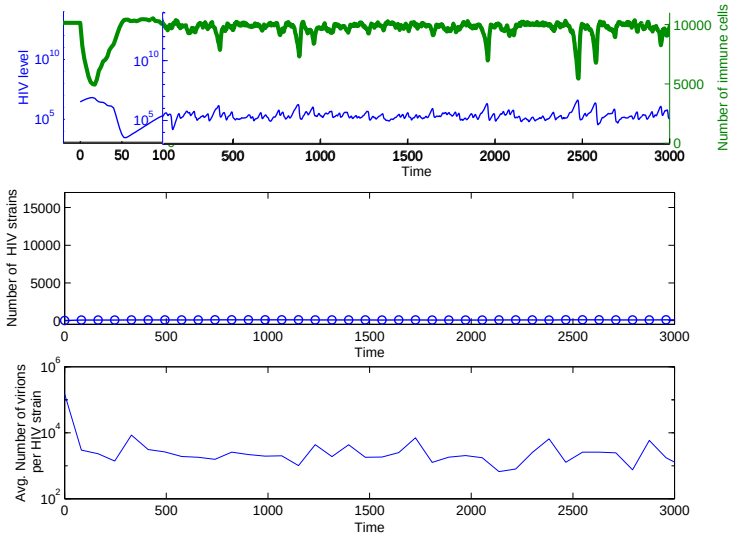

Figure 5: Merely by raising the efficiency of immune cell reaction to HIV at the different sites we can bring about a time course suggesting the progression of HIV in long-term latents [23].

become operative. Thus the time unit for one interaction in the shape space is the time needed for a single strain to establish itself. The time scale of the entire disease is the time necessary for evolving a macroscopic number of strains. Therefore we expect that the time scale of the entire disease will relate to the time scale of new strain creation as the time scale of the strains relate to the individual virion division time. The actual numbers are indeed (13 years/ 2 weeks) = (2 weeks/hours).

3 Conclusions

The main success of the present model is the **natural** emergence of a hierarchy of very different dynamical time scales. The very long-term decrease in immune (CD4+ T) cells count cannot be explained by a simple dynamic system. The transition from the microscopic time scales (hours) to the macroscopic time scales (years) requires a profound explanation. A simple dynamical system would require extreme fine tuning of its parameters in order to achieve such a transition[2, 3]. We propose a mechanism that can bridge between the microscopic and macroscopic time scales, that does not need fine tuning. The transition can be expressed best by representing the evolution of the system in the shape space (the strain of the virus), rather than the real space (the location of the virus in the organism). The relavent unit of time step for the operations in shape space is the time it takes for a strain to reach a macroscopic concen-

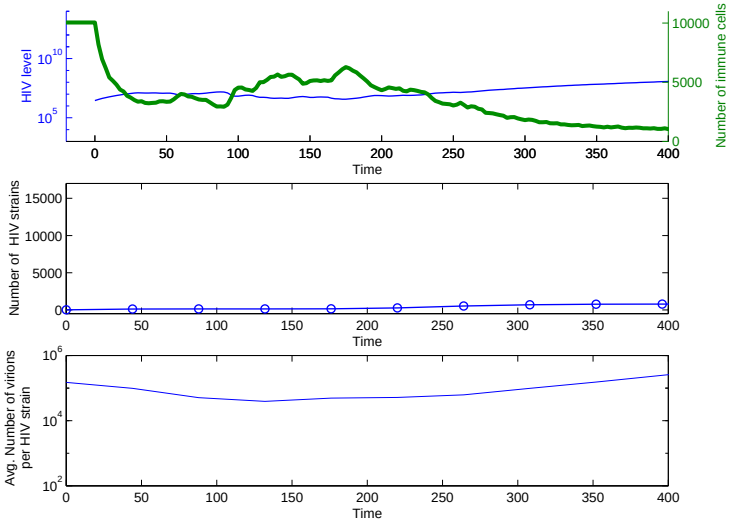

Figure 6: By decreasing the efficiency of immune cells we arrive at a scenario where already in the first acute phase we witness a full-fledged outbreak of AIDS. This is reminiscent of empirical evidence to the fact that quick progressors of HIV have a less flexible immune system and thus succumb to the disease with less strains of the virus in their bloodstream [25]. (Note that since death is so rapid the time course is only measured untill the colapse of the immune system around day 400).

tration and therefore have a significant probability to generate a mutant. This time step is of the order of weeks and not of hours. The evolution of the disease takes a few hundred time steps. i.e a few hundreds of weeks.

The mechanisms operating at the short times and at the long times are completely different. At the microscopic level the mechanism is the recognition and the destruction of the virions by the immune cells. The short time scale evolution of the disease is similar to any other disease. The long scale evolution of HIV infection is based on the competition between localized (in shape space) processes and global processes. To be precise the evolution is due to the spread of the virus strains across the shape space. In the initial acute phase most of the viral load is distributed between a small number of localized virus strains. At the last stages of the disease the viral load is distributed between a large variety of many strains. The immune cells manage to destroy locally every particular virus strain within a couple of weeks from its emergence. However as the number of strains at each given moment increases, the virus succeeds to destroy an increasing amount of immune cells. Thus locally the virus looses every battle. Yet in the end the shape space is filled with a multitude of small but numerous strain populations. At that point the virus wins the war by killing more immune cells than it activates.

In short: During the latent stage every virus strain looses every battle since it is activating the cells that can destroy it. Transition to AIDS occurs when the combined contemporary virus population wins the war by killing in total more immune cells than the sum of cells it activates.

Acknowledgment

We acknowledge Professor Zorzenon dos Santos for sharing with us the content of reference 3 before publication.

Appendix A - Acute phase

Imagine one has a lattice containing V nodes out of which N are occupied by the strains that constitutes the initial infection. We assume that the population of each initial infection strain is large enough that if the immune system generates randomly an immune cell in this site (A cell with a complementary shape to that virus strain) then that cell will discover this strain with probability 1. The probability rate for generating in a given lattice site an immune cell is λ. Therefore the probability rate for discovering one of the strains is $N\lambda$. Thus the average time it takes the immune system to detect the first strain in the initial infection is $\frac{1}{N\lambda}$. Once this strain was discovered the probability rate to discover one of the remaining (N-1) strains is $(N-1)\lambda$. This means that the time it takes to discover a second strain is $\frac{1}{(N-1)\lambda}$ and so on. Thus the average time it will take for the immune system to discover the N strains is: $\frac{1}{lambda}\Sigma_1^N \frac{1}{i}$ which is approximately $ln(N)\lambda$. As long as the virus strain is undetected by the immune system it can proliferate freely. Therefore the strain discovered last had the most time to proliferate. The factor by which it grew more than a single strain infection is :

$$e^{\frac{ln(N)-1}{\lambda} * \tau_V * C_{total}} \cong N^{\frac{\tau_V * C_{total}}{\lambda}} \quad (1)$$

Appendix B - Transition to AIDS

In this appendix we estimate the conditions for the final collapse of the immune system, when it fails to react appropriately to local virus strains. The dynamics of the population of the immune cells in a given site in the shape space is dominated by 2 parallel processes:

- Proliferation due to the activation of the immune cells by the interaction with the local (in shape space) virus strain ($\tau_C V_i$)(item 1).

- Random global destruction by arbitrarily shaped virus strains ($d_C V_{tot}$) (item 4).

An immune strain can increase its population if its proliferation rate is higher than its destruction rate. $\tau_C V_i > d_C V_{tot}$. In other words we need the ratio between local virus concentration and global virus concentration to be : $\frac{V_{tot}}{V_i} < \frac{\tau_C}{d_C}$. If we have N virus strains proliferating in the system, we can assume that their population are of the same order of magnitude, and estimate $\frac{V_{tot}}{V_i} = N_{strains}$. Thus in order for an immune strain to be able to rise its concentration and react appropriately against the corresponding virus strain One needs the number of virus strains not to exceed : $N_{strains} = \frac{\tau_C}{d_C}$. If one assumes that the virus population is not equally divided between strains the inequality is even more stringent.

Appendix C - Discretization vs Continuous Differential Equations

The evolution of a dynamical system can be expressed by 2 types of models:

1. Ordinary Differential Equations (ODE) that simulate the evolution of the average population under the assumption of spatial homogeneity.

2. Microscopic simulation (MS) models, that compute each reaction separately.

The ODEs have the advantage of being cheap in CPU time. They enable us to simulate precisely the system when its concentration is very high, but fail to describe the stochastic aspects of the system. The MS takes into account the stochastic effects and describes precisely the discrete aspects of the agents and of the strains. However MS is very inefficient if the number of agents and the probability for reaction are high.

In the present model most of the sites are basically empty. However there is a relatively small number of sites occupied by a macroscopic number of virions and immune cells. This special situation invalidates both the possibility to use continuity assumption (ODE), and discrete operations (MS).

We solved this problem by using a hybrid model. This model computes the probability for interaction between every 2 agents at every site on the lattice in a given time interval. If this probability is higher than a threshold (30) then the number of agents created or destroyed is computed in a deterministic way using an ODE formalism **for this site**. If on the other hand the probability

for a reaction is lower than the threshold the number of new agents created or destroyed is computed in a discrete stochastic way.

This is a particular application of the hybrid models we developed [18, 19, 20, 21].

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